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Selecting ventilator settings using INVENT, a system including physiological models and penalty functions

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Abstract. This paper describes INVENT, a system for selecting ventilator setting based on physiological models and penalty functions. The models and penalty functions included in INVENT are first described followed by an example of the use of the system in selecting ventilator settings for a patient residing in the intensive care unit. For this patient, the advice given by the system is shown to be reasonable and consistent with clinical opinion.

1 Introduction

Mechanical ventilation of a patient is a task which can be seen as having three logical steps: 1) assessment of the patient's pathophysiological state, for example impaired lung function, circulation or increased metabolic needs; 2) predictions of how changes in ventilator settings affect patient variables that if not controlled can cause further damage to the patient's physiology; and 3) selection of ventilator settings that are optimal in the sense of minimising damage to the patients physiology.
This paper describes the intelligent ventilator (INVENT), in which the first two steps, assessment of pathophysiology and prediction of the effects of changes in ventilator settings, are assisted by using physiological models of oxygen (O_2) and carbon dioxide (CO_2) transport, and lung dynamics. The third step is accomplished by assigning penalty functions to poor oxygenation, acidosis or alkalosis, and lung damage due to barotrauma, atelectasis or oxygen toxicity.
The paper first describes the physiological models and the penalty functions, followed by a description of how INVENT can assist in selecting ventilator settings.

2 Physiological models

2.1 The oxygen model

Figure 1 illustrates the model of oxygen transport [1,2] implemented as part of INVENT. The model includes compartments describing oxygen in the alveoli and blood, and equations describing alveolar ventilation, circulation, oxygen binding to haemoglobin and oxygen consumption. The model contains two parameters (shunt, R_{sh}) describing abnormalities of O_2 transport i.e. the shunting of pulmonary blood (shunt) and the resistance to oxygen diffusion (R_{dif}).

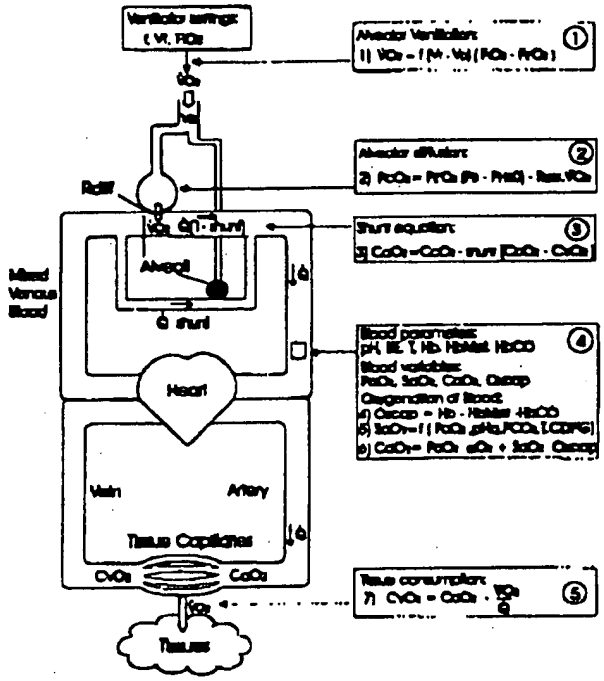

Fig 1. The Oxygen model

The equations included in the oxygen model are illustrated in the 5 boxes of figure 1. Eqn. 1 describes oxygen flow into the alveoli ($\dot{V}O_2$) in terms of the fraction of oxygen inspired (FIO_2) and expired ($F\bar{E}O_2$) and the alveolar ventilation, which is calculated as the difference between tidal volume (V_T) and dead space (V_D) multiplied by respiratory frequency (f). Eqn. 2 calculates the partial pressure of oxygen in the lung capillaries (PcO_2) as the partial pressure of oxygen in the alveoli ($PAO_2 = F\bar{E}O_2 (P_B - P_{H2O})$), minus the drop in oxygen pressure from alveoli to lung capillaries due to the diffusion resistance (R_{diff} $\dot{V}O_2$). Eqn. 3 is the shunt equation and describes the concentration of oxygen in the arterial blood (CaO_2) when blood from the lung capillaries (CcO_2) is mixed with a fraction (shunt) of venous blood ($C\bar{v}O_2$). Eqn. 4 calculates the oxygen capacity of the blood (O_2cap) when the total hemoglobin concentration (Hb) is adjusted for its abnormal forms (HbMet, HbCO). Eqn. 5 is an implementation of the oxygen dissociation curve (ODC) [3] adjusted for the pH, partial pressure of carbon dioxide (PCO_2), temperature (T) and concentration of 2,3-

Diphosphoglycerate (CDPG) in the blood. Eqn. 6 describes the concentration of oxygen in arterial blood (CaO_2) as the sum of oxygen bound to hemoglobin ($O_2cap * SaO_2$), and oxygen physically dissolved ($PaO_2 * \alpha O_2$). Eqn. 7 is the Fick equation and calculates the venous oxygen concentration (CvO_2) as the arterial oxygen concentration (CaO_2) minus the drop in oxygen concentration due to consumption by the tissues.

In addition two differential equations are used to describe the mass balance of oxygen in the alveolar and blood compartments, and hence the dynamics of the oxygen system. Oxygen reaches equilibrium rapidly after ventilatory perturbation (≈ 2-5 minutes) so that the oxygen model included in INVENT is implemented in its steady state form.

The oxygen model can be used in two ways: as a diagnostic tool to estimate values of shunt and R_{aw}, and as a prognostic tool, to predict the effects of changing ventilator settings on oxygenation. Estimates of the shunt and R_{aw} parameters can be obtained from data obtained in the clinical setting i.e. measurements of ventilation and blood gases when inspired oxygen fraction is varied in four steps, achieving arterial oxygen saturations in the range 90-100%. Previous validation of the model has shown it to give a good fit to data from normal subjects and patients following cardiac surgery [2].

2.2 The carbon dioxide model

Figure 2 illustrates the physiology included in the model of carbon dioxide (CO_2) transport implemented as part of INVENT. This model includes compartments representing CO_2 in the alveoli, blood and tissues, and equations describing alveolar ventilation, circulation, carbon dioxide production, and the binding of CO_2 in blood, interstitial fluid, and tissues.

Alveolar ventilation, circulation, and carbon dioxide production are described using equations similar to equations 1 and 7 of the oxygen model, i.e. an equation describing CO_2 flow out of the alveoli, and the Fick equation for CO_2, respectively

$$\dot{V}CO_2 = f\,(V_T - V_D)\,(PE'CO_2 - FICO_2)$$

$$CvCO_2 = CaCO_2 - (\dot{V}CO_2 / \dot{Q})$$

where $CvCO_2$, $CaCO_2$ represent the total CO_2 concentration in the arterial and venous blood i.e. that transported as CO_2 and bicarbonate (HCO_3).

The CO_2 model implemented in INVENT includes some 70 equations which can predict the effects on acid-base chemistry of changes in ventilation. This large number of equations is due to the complexity of the acid-base chemistry. For the sake of brevity this paper includes a description of the physiology included in the model rather than the model equations. A more detailed description of the acid-base chemistry equations are found in Rees et al. [4, 5].

Only a small fraction of CO_2 is transported in the blood in solution, the majority being transported as bicarbonate (HCO_3) in a complex set of reaction equations which buffer hydrogen ions (H) and hence regulate the acid-base chemistry of the blood. These

equations are represented in figure 2. For the plasma fraction of blood two reaction equations are required representing CO_2 conversion to HCO_3 (eqn. 1), and the buffering of H by non-bicarbonate buffers (NBB), including phosphate and protein (eqn. 2). In the erythrocyte fraction of blood equations are required representing CO_2 conversion to HCO_3 (eqn. 3), the competitive binding of H and O_2 to the haemoglobin molecule ($HbNH_2$) (eqns. 4a and 4b) known as the Bohr/Haldane effect, and the binding of CO_2 with haemoglobin to form carbamate (HbNHCOO) (eqns. 5a and 5b). Eqns. 5a and 5b also describe the competitive binding of O_2 and CO_2 to the haemoglobin molecule.

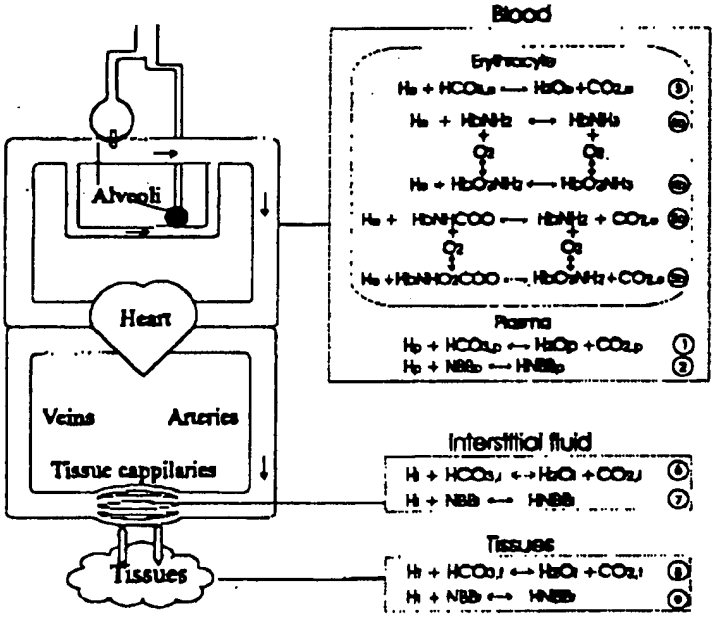

Fig 2: The carbon dioxide model

The combined plasma and erythrocyte model represents the acid-base chemistry of the blood. This model is a modification of that reported by Rees et al. [4,5] extended by including the Bohr/Haldane effect and the carbamate buffer. This acid-base model has been validated by comparing pH, PCO_2 titration curves constructed using the model with those constructed using the Siggaard-Andersen curve nomogram [6] which describes the acid-base chemistry of the blood under *in vitro* conditions. The model of

acid-base chemistry has been shown to reproduce values obtained using this nomogram [4,5].
Unlike oxygen, significant quantities of CO_2 are present in the interstitial fluid and tissues. The model of CO_2 transport included in INVENT represents interstitial fluid as a single pair of bicarbonate non-bicarbonate buffers (eqns. 6 and 7, figure 2), similar to those in plasma. Tissue stores of CO_2 are large amounting to some 120 liters [7]. These stores are highly heterogeneous with experiments of duration of weeks necessary to investigate the turnover of the slowest pools [7]. It is likely that the majority of tissue involved in the rapid exchange of CO_2 is muscle [7,8]. The CO_2 model included in INVENT therefore includes a representation of the tissue buffering as a single pair of bicarbonate non-bicarbonate buffers corresponding to muscle (eqns. 8 and 9, fig. 2).
The equations describing acid-base chemistry in the blood, interstitial fluid, and tissues have been combined with 5 differential equations used to describe the mass balance of total CO_2 (tCO_2) in the alveolar, blood, and tissue compartments, and the mass balance of Base Excess, and O_2 in the blood. The dynamic model of CO_2 transport including the acid base chemistry and the differential equations has been shown [5] to reproduce the characteristic two exponential response of $FE'CO_2$ to hypo-ventilation, with half lives of the exponentials equivalent to those reported [9] during hypoventilation experiments.
The CO_2 model included in INVENT is implemented in its steady state form where the differential equations are set to zero. The model can be used to predict the steady state values of acid-base chemistry variables 0.5-2 hours following a change in ventilation, after which CO_2 in the muscle should be at equilibrium with the blood.

2.3 The lung dynamics model

INVENT includes a simple one compartment model of lung dynamics, where the relationship between tidal volume V_T and the change in pressure in the lungs (ΔP) is described by the equation

$$V_T = \Delta P \ Comp \ (1 - e^{-it/te})$$

where: ΔP is the change in pressure in the lung i.e. the positive inspiratory pressure (PIP) minus the positive end expiratory pressure (PEEP); Comp is the compliance of the lung; 'it' is the inspiratory time and can be calculated from the respiratory frequency (f) and the inspiratory:expiratory ratio (I:E); and 'te' is the time constant which is calculated as the product of the compliance and resistance of the lung.

3 Penalty functions

The physiological models described in section 2 can be used to asses the patient's pathophysiological state and to predict the effects of changing ventilator settings. To

select optimal ventilator settings, i.e. those which minimise the damage to the patient's physiology, it was necessary to specify five penalty functions. Figure 3 illustrates the five penalty functions implemented in INVENT to describe the penalty associated with barotrauma (fig. 3a), atelectasis (fig. 3b), acidosis and alkalosis (fig. 3c), poor oxygenation (fig. 3d), and oxygen toxicity (fig. 3e). Penalties were assumed to be additive, and based on input from experienced clinicians the penalty curves were scaled accordingly.

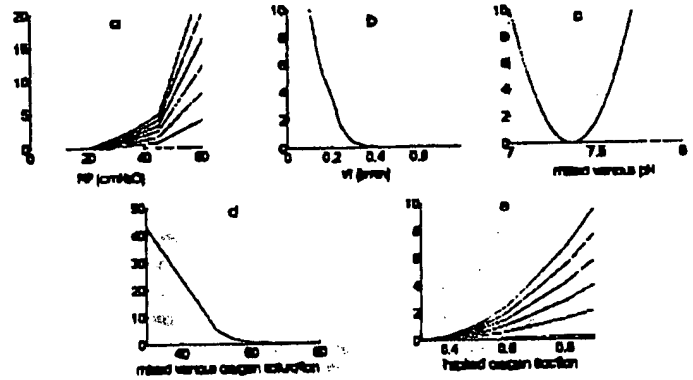

Fig 3. Penalty functions included in INVENT. Penalty is represented on the y-axis. The five functions represent penalty due to: a) barotrauma, as a function of peak inspiratory pressure (PIP). The individual curves represent penalties incurred for the respiratory frequency, f = 5, 10, 15, 20, 25, 30; b) atelectasis, as a function of tidal volume (V_T); c) acidosis and alkalosis as a function of mixed venous pH; d) poor oxygenation as a function of mixed venous oxygen saturation; and e) oxygen toxicity as a function of inspired oxygen fraction (FiO_2). The individual curves represent penalties incurred for a number of hours (h) at the FiO_2 level. h = 1, 8, 16, 24, 32, 40.

4 Selecting ventilator settings using INVENT

Figure 4 illustrates the user interface of INVENT. From this interface it is possible to perform the three logical steps required to select ventilator settings i.e. patient assessment; predicting the outcome of changing ventilator settings; and selecting the appropriate ventilation. These three stages are now illustrated using data from a patient (ER) residing in the ICU.

The user interface illustrated in figure 4 includes data from patient 'ER'. This patient required mechanical ventilation because of lung damage due to inspiration of bile acid, and was ventilated at a high inspired oxygen fraction FiO_2 = 0.48, with application of positive end expiratory pressure PEEP = 6 cmH_2O.

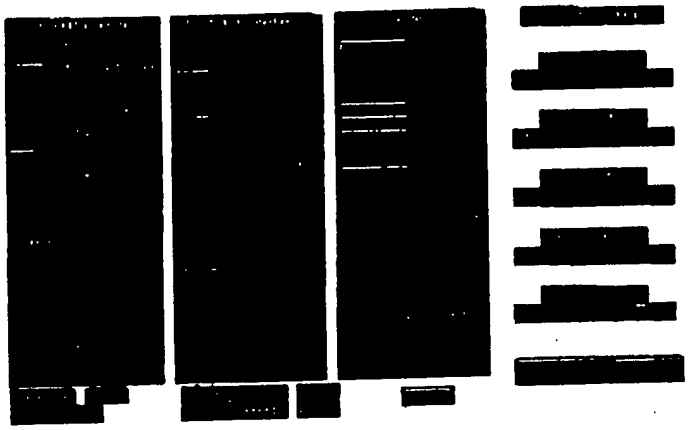

Fig 4. Invent: The user interface, including data from patient ER

Other ventilator settings at the time of study were V_T = 0.4 l, f = 15.1 breaths/min, and an inspired: expired ratio of 0.5. These settings have been input into column 4 of the user interface as illustrated in figure 4.

Further measurements available for this patient were: PIP = 29.5 cmH_2O, temperature T= 39 °C, end tidal oxygen fraction $F_E\hat{O}_2$ = 0.4, end tidal carbon dioxide fraction $F_E\hat{C}O_2$ = 0.064, arterial blood gas measurements pHa = 7.421, P_aCO_2 = 6.19 kPa, P_aO_2 = 10.6 kPa, S_aO_2 = 96.4 %, Hb = 6.1 mmol/l, HbCO = 0 %, HbMet = 1.01 %, and central venous blood gas measurements pH_v = 7.404, P_vCO_2 = 6.55 kPa, P_vO_2 = 5.0 kPa, S_vO_2 = 74.8 %. These measurements were used to asses the patients current state i.e. to estimate values for the patient parameters in column 1 figure 4. Values of T, Hb, HbCO, and HbMet were input directly into column 4. In addition the measurements were used to calculate values of compliance (Comp) and resistance (Res) oxygen consumption ($\dot{V}O_2$), cardiac output (Q), carbon dioxide production ($\dot{V}CO_2$), and the mixed venous pH (pH_v) and PCO_2 (P_vCO_2), these calculations being performed using the physiological models described in section 2. The results of these calculations are shown in column 1 figure 4.

Values for the remaining parameters in column 1 i.e. shunt, R_{aw}, CDPG, h and dead space (V_D) were estimated as follows: V_D cannot be estimated and was assumed to equal 0.15 l; the hours at a particular O_2 level (h), necessary to quantify the penalty associated with oxygen toxicity was specified by the clinician. The three other parameters shunt, R_{aw}, CDPG cannot be estimated from data measured at a single oxygen fraction, and required a procedure where inspired oxygen fraction is varied in four steps [2]. Whilst estimates of a single parameter 'effective shunt' can be obtained from data measured at a single oxygen fraction, this single parameter model does not give a good fit to data at varying inspired oxygen fractions. A two parameter model

(shunt, R_{aw}) of lung function is therefore required to describe the effects of changing inspired oxygen on the ventilator.
The clinician is guided through the estimation of CDPG shunt, and R_{aw} by clicking on either of the shunt, or R_{aw} buttons on the user interface, after which they are presented with the parameter estimation screen illustrated in fig 5.

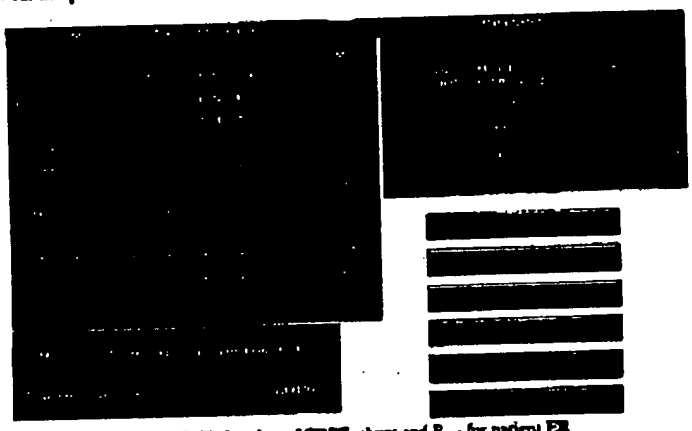

Fig. 5: Estimation of CDPG, shunt and R_{aw} for patient ER

Fig. 5 illustrates data from patient 'ER' at 4 different settings of inspired oxygen fraction (0.32, 0.38, 0.48 and 1). At each setting measurements of ventilation and arterial blood gases were recorded. The six push buttons in fig. 5 then perform the following functions enabling parameter estimation. The first and second enable estimation of CDPG (normal value = 5 mmol/l) from the oxygen dissociation curve which can then be plotted. The third button plots curves of inspired oxygen against both arterial oxygen saturation and pressure. This is done for initial estimates of the two parameters shunt, R_{aw}, giving the user an intuitive feel for the correct range of these parameters. The next two buttons estimate Shunt, R_{aw}, and plot the same curves for the model estimated parameters. These curves are illustrated in fig. 6 for patient ER showing a good fit of the model to the data.
The second column of the user interface illustrated in figure 4 contains the models predictions for mixed venous pH (pHmv), mixed venous oxygen saturation (SvO_2) and PIP given the patient parameters and ventilator settings. Full descriptions of oxygenation (arterial and mixed venous O_2 saturation and pressure) and acid base status (arterial and mixed venous pH and CO_2 pressure, and $PaCO_2$) can be obtained by clicking on the respective buttons in this column. The third column describes the five individual penalties and the total penalty for these model predictions. The total penalty for patient ER was 1.966, this being largely due to barotrauma, because of an elevated PIP, and oxygen toxicity due to the high inspired oxygen fraction.

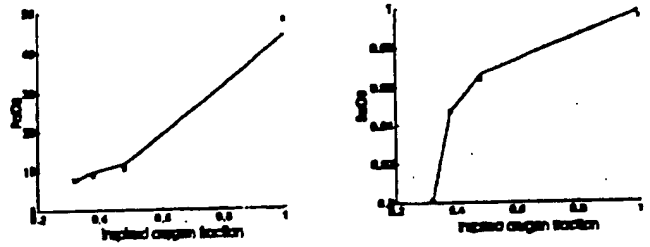

Fig 6. Curves fitted to arterial oxygen saturation and pressure using the oxygen model. Crosses indicate data from a mechanically ventilated patient in the ICU (ER)

Included on the user interface screen is an "Optimal ventilator settings" button which finds the values of tidal volume, respiratory frequency, and inspired oxygen fraction which minimise the total penalty. Figure 7 illustrates the optimal ventilator settings suggested by INVENT for the patient ER.

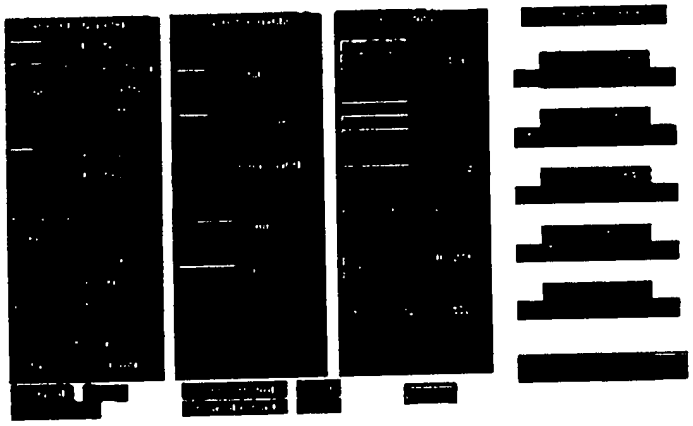

Fig.7 User interface illustrating ventilation suggested by INVENT for patient ER

The system suggests a 10% reduction in inspired oxygen fraction with small changes in tidal volume and respiratory frequency. A 10% reduction in inspired oxygen is clearly beneficial to the patient and results in a predicted change of arterial oxygen saturation from 96.6% to 94.1% which is minor, and within the limits of clinical acceptability. The advice provide by INVENT was consistent with clinical opinion, at the time of study the clinician thought the patient was improving and was considering lowering the inspired oxygen fraction.

4 Conclusions

This paper has presented an approach to automating the three logical steps in selecting ventilator settings i.e. patient assessment, prediction of the effects of changing ventilator settings, and selecting optimal ventilator settings.
This approach has been implemented in the system INVENT, a system which includes physiological models, and penalty functions. The application of the system has been illustrated with data from a patient residing in the ICU.
Whilst the system has been shown to provide reasonable advice in this patient a number of further developments are required if it is to achieve wider applicability. In particular, the current system does not include relationships between pressure in the lung (PEEP, I:E ratio, PIP) and lung parameters (shunt, R_{aw}), or between cardiac output and oxygen saturation. The current system is also limited to those patients with no spontaneous breathing.
Despite these limitations, this paper illustrates the potential for INVENT to provide useful advice on optimising ventilator settings for patients in the intensive care unit.

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